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Sulthiame in refractory paediatric epilepsies: An experience of an 'old' antiepileptic drug in a tertiary paediatric neurology unit

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ABSTRACT

Purpose: Sulthiame is an old antiepileptic drug primarily used in a few European countries for the treatment of benign epilepsy of childhood with central temporal spikes. Other studies suggest that it might be effective in children and adults with a range of refractory seizure types.
Methods: A retrospective case note review was undertaken to evaluate the efficacy and safety of sulthiame as adjunctive therapy in children with refractory epilepsies.
Results: Twenty patients (10 female) were evaluated, aged 10.7 (range 2.1–17) years. The median duration of treatment with sulthiame was 18 (range 2–37) months. Fifty five percent of patients showed at least a 50% reduction in seizure frequency and two patients were seizure-free at the end of follow-up. Patients with focal seizures responded best. Seven patients reported side effects, leading to withdrawal of the drug in two (10%).
Conclusion: Sulthiame was reasonably effective and well-tolerated in a heterogeneous group of 20 children with refractory epilepsies. Although an 'old' antiepileptic drug it should be considered in a similar population.

1. Introduction

Sulthiame (STM), a carbonic anhydrase inhibitor, became established as an antiepileptic drug (AED) in the treatment of partial (focal) epilepsies in the 1950s. Over the subsequent half-century it has been reported to be effective as adjunctive therapy or monotherapy in benign partial epilepsy with centro-temporal spikes (BECTS),[1,2] other, non-BECTS focal epilepsies,[3] children with refractory epilepsy[3–5] adults with refractory epilepsy and learning difficulties,[6] adults with refractory focal and/or secondarily generalised seizures,[7] juvenile myoclonic epilepsy and other myoclonic seizures,[3,8] infantile spasms,[9] Rett syndrome[10] and continuous spike waves in slow-wave sleep.[11] The drug has also been reported to either normalise, or markedly improve the abnormal electroencephalographic (EEG) activity in BECTS.[12,13] There have been conflicting reports of its effect on cognitive function.

Studies in the late 1960s showed that the metabolism of phenytoin was inhibited by STM resulting in an elevation of phenytoin blood levels and possible toxicity.[14] This led to the perception that STM might have no independent anticonvulsant efficacy which was only partly refuted following publication of a double-blind randomised trial of STM and phenytoin[15] and limited data that it may have independent sodium channel-blocking (and therefore anticonvulsant) activity.[16,17] This perception, together with concerns over its adverse side-effect profile led to the marked decline of the use of STM in routine practice, other than in a few countries in Europe. This might in part explain the relative scarcity of reports of its use in treating children with refractory epilepsy.[3–5]

The aim of this paper is to report the efficacy and safety of STM in a heterogeneous group of children with refractory epilepsies.

2. Patients and methods

This was a retrospective study on the use of STM in children with refractory epilepsy. Patients were identified from the epilepsy clinics of three consultant paediatric neurologists at this institution between July 2007 and August 2010. A patient was considered to be refractory if they had failed to respond to at least two previously prescribed AEDs in appropriate and optimal doses and who had experienced at least one seizure per month in the 12 months prior to the introduction of the drug.

Medical records were reviewed and clinical information was recorded on a standard proformas including age of the onset of epilepsy; seizure type; epilepsy syndrome; underlying cause; presence of learning difficulties; prior and current AED history;

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maximum doses of STM; seizure frequency, side-effects and duration of treatment.

The epilepsy syndromes were classified according to the 1989 International League Against Epilepsy (ILAE) classification.

The efficacy of STM was assessed based on seizure frequency determined by seizure diaries completed by caregivers. The baseline seizure frequency was obtained from the case notes at the time STM was first prescribed. Response rates were assessed at the following times: three and 12 months after starting STM, at the time any decision was made to withdraw STM and at the last recorded follow-up for those who remained on the drug. A judgement on the relative change in seizure frequency was assessed from the case notes or clinic letters and was documented as follows: seizure free (defined as no seizures for a minimum of 12 months); >50% reduction in seizure frequency; some improvement (25–50%); no significant response (0–24%) and increased seizures.

Tolerability was assessed by recording any documented unwanted side-effects and reasons for discontinuation of STM were recorded.

Laboratory investigations were undertaken if clinically indicated. Routine EEG recordings and neuro-cognitive assessments were not obtained sequentially during the patient's treatment with STM; however, repeat EEGs were undertaken in patients with continuous spike wave activity in slow wave sleep.

Data analysis was descriptive.

3. Results

3.1. Patient characteristics

Twenty children (10 females) were evaluated in this study. Patients were classified according to seizure type (generalised, focal or mixed), aetiology (idiopathic, cryptogenic or symptomatic) and epilepsy syndrome (Table 1). Fourteen of the 20 (70%) patients had learning difficulties, severe in five; 18 of the 20 patients had undergone formal assessments of cognitive function including with age-appropriate Wechsler examinations.

Eighteen patients had failed to achieve acceptable seizure control on a minimum of three previous AEDs (median 7.7; range 2–9); two patients had received only two AEDs prior to commencing STM. Sulthiame was started as adjunctive therapy in all 20 patients. The median number of concomitant AEDs used was 1.2 (range 1–3) with the most commonly prescribed being valproate and clobazam (Table 2). During the study, concomitant antiepileptic medication was able to be withdrawn in three patients.

One patient had undergone a frontal, fronto-parietal and temporal resection four months prior to the introduction of STM for extensive cortical dysplasia. Three patients had undergone insertion of a vagal nerve stimulator (VNS) four, six and eight months prior to the commencement of STM and one patient had been started on a ketogenic diet five months before the introduction of STM, without any improvement in seizure control.

The median duration of STM treatment was 18 months (range 2–37 months). The median final maintenance dose was 8.2 (range 2–12) mg/kg/day.

3.2. Efficacy

Three patients (15%) discontinued STM before three months, two because of an increase in seizure frequency (focal and secondary generalised tonic–clonic) and one patient reported increased focal seizures and unacceptable drowsiness. One patient was followed up for only two months and two weeks and excluded from the analysis. The median length of follow-up for the remaining 16 patients was 19 (range 4–37 months) months.

Fourteen of the 16 patients (70%) demonstrated a reduction in seizure frequency of >50% at the first follow-up period (three months). However, seizure control subsequently deteriorated in four of these 16 patients (20% of the whole group) at eight, 11, 18 and 20 months after the introduction of STM and the drug was withdrawn.

Two patients showed a seizure reduction of 25–50%.

No patient developed a new seizure type during the study.

Three patients (15%) became seizure free, two remaining so following discontinuation of concomitant AEDs. One was an 11 year old girl with learning difficulties, focal cryptogenic epilepsy and continuous spike wave activity in slow wave sleep (CSWSS) who had been seizure-free for 14 months at the end of the study and on a maintenance dose of 15 mg/kg/day. Overnight EEG undertaken two months after starting STM showed resolution of CSWSS. The other patient was an 11 year old boy, with cryptogenic focal epilepsy who had been seizure-free for 16 months at the end of the study and receiving a maintenance dose of 7.5 mg/kg/day. Seizure-freedom was lost in the remaining 13 year-old boy after 11 months but seizure-reduction was still >90% at 19 months on a maintenance dose of 6.5 mg/kg/day when the study ended.

Patients who showed the best response with >50% reduction in seizures, included those with focal cryptogenic epilepsy (five of six patients, 83%) and focal symptomatic epilepsy (six of nine patients, 66%) (Table 3). Only two of the four patients with a generalised epilepsy, including one patient with Lennox-Gastaut syndrome showed >50% reduction; however, both patients subsequently showed deterioration after 18 months of treatment.

Table 1
Demographic and clinical characteristics of the 20 patients.

Characteristic	*N* (%)
Mean (range) age in years	10.7 (2.1–17)
Generalised seizures:	4 (20)
Idiopathic	1 (5)
Myoclonic-astatic epilepsy	
Cryptogenic	2 (10)
No syndrome	1
Lennox-Gastaut syndrome	1
Symptomatic	1
CDKL5 mutation	
Focal seizures:	15 (70)
Cryptogenic	6 (30)
Symptomatic	9 (45)
Focal cortical dysplasia	6 (30)
Tuberous sclerosis	1
Porencephaly	1
Periventricular leucomalacia	1
Mixed (generalised and focal seizures):	1 (5%)
Dravet syndrome	1

Table 2
Concomitant antiepileptic drugs in the 20 patients.

Antiepileptic drug	Patient number (%)
Valproate	6 (30)
Clobazam	6 (30)
Levetiracetam	5 (25)
Carbamazepine	4 (20)
Lamotrigine	2 (10)
Nitrazepam	1 (5)
Oxcarbazepine	1 (5)
Phenytoin	1 (5)
Rufinamide	1 (5)
Zonisamide	1 (5)
Topiramate	1 (5)

Table 3
Response by seizure type.

Seizure type	Number of patients	>50% reduction	25–50% reduction	0–24% reduction	Increase in seizure frequency
Focal	16	14	1	0	1
Secondary GTC	14	11	1	1	1
Absences (atypical)	6	1	–	5	–
Myoclonic	5	–	1	2	2
Tonic	3	–	–	2	1
Primary GTC	2	1	–	–	1
Atonic	2	–	–	1	1

GTCS: generalised tonic–clonic seizures.

Finally, the small number of patients and large number of concomitant AEDs prescribed precluded any conclusion as to whether any specific combination with STM was more or less effective.

3.3. Tolerability

Thirteen (65%) of the 20 patients and 11 (55%) remained on treatment at 12 months and at 37 months respectively, on completion of the study. Nine (45%) patients discontinued treatment; four (20%) because of lack of therapeutic benefit; two (10%) an increase in seizure frequency; two (10%) because of an increase in seizure frequency and side effects; and in one (5%) because of lack of efficacy and side effects; in one (5%). Side-effects which contributed to the withdrawal of STM in the two patients included cognitive impairment and drowsiness; the maximum dose of STM in these patients was 6.2 and 7.4 mg/kg, respectively.

Seven patients (35%) reported at least one unacceptable and unwanted side-effect, most of which were mild and which resolved on reduction of dosage other than the two patients described above. The most frequently reported side-effect was drowsiness (two patients, 10%); one patient each complained of cognitive slowing, hypersalivation, breathlessness and tachypnoea and diarrhoea. The maximum dose of STM in patients who experienced side effects was 9.8 mg/kg.

4. Discussion

Despite the introduction of at least 10 new anti-epileptic drugs since 1990, at least 25% of children with epilepsy remain refractory. There may be a reluctance to prescribe older AEDs because of the perception that they may have been less effective or may have been associated with unacceptable adverse side-effects, or both. This phenomenon may have applied, and still apply, to STM. Previous reports on the efficacy of STM and its continuing use in a number of countries encouraged the epilepsy unit in this institution to prescribe the drug in children with refractory epilepsy.

In this retrospective analysis of the STM-treated patients, 13 patients (65%) showed greater than 50% reduction in seizure frequency at one year follow-up. With longer follow-up, the drug's efficacy and tolerability was maintained in 11 (55%) patients, including the two patients who became seizure-free (and who had remained so for over 12 months at the end of follow-up). This is higher than the 42% responder rate observed in the one adult study undertaken in a larger population with predominantly focal seizures and with heterogeneous aetiologies and learning difficulties[6] and 17.8% in 28 adult patients treated in a German study.[7]

A Japanese study (written in Japanese) reported 26 children aged less than 18 years with intractable generalised and focal epilepsies who received STM in doses of 4–14 mg/kg/day.[5] Two patients became seizure free and eight demonstrated a >50% reduction in seizure frequency; however, six of these 10 patients developed "tolerance" with loss of seizure control. A study undertaken by the national epilepsy centre in Norway and published in abstract form reported that seven (46%) of 15 children with refractory epilepsy treated with STM showed >75% reduction in seizures; there was no information on duration of follow-up and tolerability.[4] In a retrospective study of 125 children with different types of epilepsy treated with STM, four of seven patients with symptomatic focal epilepsy showed >50% seizure reduction, but there was no further information on these patients.[3]

Sulthiame appeared to be particularly effective in treating focal seizures with 14 (88%) of the 16 patients with focal seizures demonstrating >50% reduction. This is similar to the adult study[6] and other paediatric studies of STM in BECTS,[1–3,13] occipital epilepsy[18] and other focal seizures/epilepsies.[3] In contrast, five of eight patients (63%) with generalised, but only two of seven patients (29%) with focal seizures showed >75% seizure reduction respectively in the Norwegian study.[4] One of our patients with learning difficulties showed resolution of CSWSS and had been seizure-free on STM monotherapy for 14 months at the end of the study.

Sulthiame has been reported to be effective in the treatment of myoclonic seizures.[3,8] This was not reflected in the five patients with this seizure type in the current study but the small number of patients precludes any meaningful comment or conclusion on this issue.

Limited data suggest that its efficacy may be related to the dose[2–4] and this was reflected in the current study; the median dose of STM in those showing >50% seizure-reduction (8.9 mg/kg) was higher than compared to the rest of the group (7.6 mg/kg). This might suggest that further dose increases may be justified, providing it is well-tolerated.

Sulthiame was well-tolerated in the current study with only two of 20 patients discontinuing the drug because of unacceptable side-effects. This retention rate is comparable to that reported for the newer AEDs.[19,20] The incidence of side effects of STM (35%) was lower when compared to an earlier study[2] but considerably higher than that observed in an adult study.[7] This could in part, reflect the fact that most of our patients had moderate or severe learning difficulties and may not have been able to verbalise the more commonly reported side-effects associated with STM (cognitive slowing and a feeling of breathlessness or tachypnoea). One patient with no learning difficulty did show some cognitive difficulties, which resolved when the dose was reduced from 12 to just under 10 mg/kg/day although the drug was subsequently discontinued because of poor seizure control. Cognitive impairment has been reported previously[21] although it has been disputed that this may have been an effect of BECTS rather than the drug itself.[22]

Side-effects seem to be dose-related.[2,15,23] This was supported by the current study; the median dose in patients who reported side-effects was slightly higher (9.8 mg/kg) than those who did not (8.2 mg/kg). The doses used in this study are higher than those used in European studies,[2,13] and particularly in those countries

(Germany, Switzerland) where STM is routinely prescribed for BECTS, but considerably lower than one of the earliest studies.[15]

This study clearly has number of limitations. First, it is retrospective and involves a small number of patients. Second, it assesses a very heterogeneous group of children which precludes any conclusion as to which seizure type (or types) is (are) most likely to respond best. Third, the study did not use any serial and formal assessments of cognitive function. Despite these limitations the results suggest that treatment with STM may be associated with a significant and sustained improvement in seizure control in children with refractory epilepsy and particularly those with refractory focal seizures.

In conclusion, STM, despite being an 'old' AED seems to have good efficacy, a relatively good safety profile, does not require blood-monitoring and could be considered as an additional treatment option in children with refractory epilepsy. However, it remains unclear as to exactly when it should be prescribed in children with refractory, and particularly focal, epilepsy.

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